REMARKS

Claims 1-3, 6, 7 and 9 have been examined and stand rejected. Claims 4, 5, 8 and 10-25 stand withdrawn from consideration. Applicants maintain their traversal of the restriction requirement, for the reasons set forth below and note that, upon allowance of the elected species claims, claims 10-18 will be rejoined and examined in the present application.

By virtue of this response, claims 1, and 7 have been amended, claims 3 and 9 have been cancelled, and new claims 26-28 have been added. Accordingly, claims 1, 2, 6, 7 and 26-28 are presently under consideration.

Support for the amendment to claim 1 is provided at *e.g.*, p. 7, lines 5-8 and p. 9, lines 16-18. Support for new claim 26 is provided at *e.g.*, p. 9, lines 5-10. Support for new claims 27 and 28 is provided at *e.g.*, page 9, lines 17-22. No amendment should be construed as an acquiescence in any ground of rejection.

Applicants address the Examiner's comments in the order made.

1. Amendment during international phase

A copy of the substitute sheet containing amended claims filed with applicants' letter of December 5, 1999 is attached.

2. Lack of unity requirement

The Examiner maintains the restriction requirement on the basis that MPEP defines a special technical as defining a contribution which each invention considered as a whole makes over the prior art. The Examiner also says that the different groups of claims are capable of different methods of manufacture, different uses and distinct from each other in that one group does not make another obvious. Applicants maintain their traverse for the reasons given previously and below.

Annex B at MPEP at p.AI-53 provides guidelines for applying unity of invention. These guidelines provide in relevant part:

> If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity of invention arises in respect of any claims that depend on the independent claims. In particular, it does not matter if a dependent claim itself contains a further invention.
>
> By "dependent" claim is meant a claim which contains all the features of another claim and is in the same category of claim as that other claim.
>
> The method for determining unity of invention under Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:
>
> (i) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for use of the said product.

Here claim 4 incorporates all the elements from claim 1 and thus constitutes a dependent claim in the same category as claim 1. According to the above guidelines, it is irrelevant whether or not claim 4 contains a further invention than claim 1. Claims 19 and 23 constitute respectively processes for manufacture and use incorporating the product of claim 1. The guidelines state that such combinations comport with unity of invention. Thus, claims 1, 4, 19 and 23 share unity of invention.

The Examiner's remarks regarding different methods of manufacture, uses and patentable distinctness are criteria for conventional restriction practice for applications filed under 15 USC 111(a) but not for unity of invention for applications filed under 35 USC 371. For these reasons, applicants maintain that the lack of unity requirement should be withdrawn.

3. Abstract

An abstract is provided on a separate sheet. This abstract is taken from the cover page of the PCT of which the present case is the US national phase.

4. Rejection under 35 USC 101 for lack of utility

The claims stand rejected as not supported by a specific asserted or a well-established utility. The Examiner says that the claims are drawn to libraries not compounds. The Examiner also says that the Examples do not illustrate uses of compounds. The Examiner cites *In re Brenner* for the proposition that use of a compound to produce other compounds to be screened for an activity was not an acceptable utility. This rejection is respectfully traversed.

Although the claims are drawn to libraries of zinc finger proteins rather than specific zinc finger proteins the facts and circumstances are very different from those of the *In re Brenner* case. The collection of compounds in *Brenner* were not known to include any examples having any known useful activities. In the present case, however, it is known that the zinc finger proteins of the claimed library have the general property of sequence-specific binding to a target sequence. The examples also demonstrate that the libraries can readily be screened using phage display techniques to isolate particular zinc finger proteins with specificity for particular target sequences. As discussed below, when one has a zinc finger protein with specificity for a particular target sequence, a variety of applications relating to detecting the target sequence or modulating its expression readily follow.

The specification expressly discloses at least three utilities including diagnostics, research tools and therapeutics (see pp. 27-32). Any of these utilities is credible given the nature and mechanism of zinc finger proteins and the state of the art. Zinc finger proteins are proteins that bind specific DNA target sequences to modulate the expression of a gene. Other reagents that perform similar functions (*e.g.*, DNA probes and antisense RNAs) are well known to be useful for such purposes. There is no reason to think that a zinc finger protein that binds a specific sequence would be less useful than a DNA probe that binds the same sequence, or that a zinc finger that modulates a gene would be less useful that an anti-sense RNA that modulates the same gene. Because the asserted

utilities are creditable for reagents such as probes and antisense RNA having analogous functions to zinc finger proteins, they are credible for zinc finger proteins too.

Although the Examples in the specification may focus on isolation of zinc finger proteins with a given binding specificity rather than illustrating uses of zinc finger proteins, the latter readily follows from the former. For example, if one has a zinc finger protein that can bind to a given target sequence, it is not difficult to see how the zinc finger protein can be used in a diagnostic assay for detecting that target sequence. The underlying principles are the same as in any other detection assay, namely, one contacts a target with a zinc finger protein, and determines whether specific binding occurs.

The Examiner's attention is also drawn to the fact that uses of zinc finger proteins, similar to those mentioned above, are disclosed by Choo *et al.* US 6,007,988 (cited later in the Office Action). Utilities disclosed in an issued patent must be presumed to be enabling and credible. These utilities are equally applicable to the zinc finger proteins of the present claims.

For all of these reasons, it is respectfully submitted that the rejection should be withdrawn.

5. Rejections under 35 USC 112, second paragraph

A). Claim 1 stands rejected because the Office Action states that the language "at least partially randomized such that the randomization extends to cover the overlap of a single pair of zinc fingers" is indefinite. The use of the expression "at least" is also alleged to be indefinite in the context of a single pair of zinc fingers.

In response, claim 1 has been amended to delete the offending terminology. Following the Examiner's suggestion, amended claim 1 and new claims 26-28 recite specific positions which can be randomized. It should be clear that randomization can occur at other positions as well.

B). The Examiner says claim 3 is indefinite in referring to one and a half zinc fingers. This phrase has been cancelled; therefore the rejection is moot.

C). The Office Action states that claims 6 and 7 lacks antecedent basis because the base claim does not recite numbered positions. In response, the base claim has been amended to provide antecedent basis for numbered positions in claims 6 and 7.

The Examiner says that the terms "may" and "possible" in claim 7 are indefinite. These terms have been deleted.

The Examiner says that claim 7 is further unclear as to the restriction imposed on the random residues in that different positions specify different amino acids. In response, the claim is intended to specify that different positions are randomized with different collections of amino acids. It is not seen what other interpretation of the claim the Examiner believes is possible.

D). The Examiner says claim 9 represents a broadening of claim 1. Claim 9 has been cancelled mooting the rejection.

6. Double patenting

Claims 1-3, 6-7 and 9 stand rejected for obviousness-type double patenting over claims 1 and 2 of Choo *et al.* in view of Ogata and Hall. Choo *et al.* is cited as disclosing

libraries of zinc finger proteins in which at least one zinc finger has a randomized allocation of amino acids. The Examiner acknowledges Choo *et al.* do not disclose a library of overlapping partially random residues. Ogata is cited as disclosing that a tandem repeat of c-myb is essential for sequence specific DNA binding. Hall is cited as disclosing that members of a nuclear hormone receptor family share a common modular structure consisting of a zinc finger domain that confers DNA binding. The Examiner takes the view that it would have been obvious to make the library of Choo *et al.* with overlapping residues because Ogata discloses that overlapping or tandem repeats are essential for sequence specific DNA binding. The Examiner says that one would have been motivated to combine the reference to make a diverse library resulting in compounds with more or increased pharmacological effects due to high specificity binding. This rejection is respectfully traversed.

The present claims are directed to libraries of zinc finger proteins in which specified positions of adjacent zinc fingers are randomized. The present application provides the insight that by simultaneously randomizing these positions in adjacent fingers, one can obtain zinc finger proteins with additional binding specificities compared to zinc finger proteins obtained by previous methods (compare specification at p. 2, lines 12-27 (discussing prior art) and p. 36, lines 20-29, discussing results obtained with the presently claimed invention). The additional specificities result because of binding interactions between adjacent fingers, and randomization of residues from both fingers is needed to encompass the full range of binding specificities.

The claims of Choo *et al.* specify libraries of DNA encoding zinc finger polypeptides having at least one zinc finger having a random allocation of amino acids at certain specified positions. The claims do not identify which positions have a random allocation of amino acids if more than one finger is randomized in such a library.

Ogata discusses a DNA binding protein with three imperfect tandem repeats and investigates the binding of the third of these to DNA. Hall merely indicates that certain hormone receptors hormone share a zinc finger.

From the above discussion, it is apparent that Ogata and Hall do not add any relevant information to that already present in the claims of Choo *et al.* Ogata may indicate that multiple zinc fingers are needed for binding, but that does not suggest the randomization of overlapping zinc fingers in the library of Choo *et al.*, especially in light of the limitations on library size disclosed in Choo *e.g.*, at column 14, lines 23-30. Hall may indicate that a common zinc finger mediates DNA binding in a receptor family, but it is well-known that zinc fingers bind to DNA. Neither Ogata nor Hall teaches simultaneous randomization of adjacent fingers in a zinc finger protein, and in particular, simultaneous randomization at the positions recited in claims 26-28. For these reasons, it is submitted that the combination of references does not teach every element of the claimed invention.

It is further submitted that the asserted motivation is insufficient to support combination of the references. "To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). The motivation must be specific and objective. In re *Dembiczak,* 50 USPQ2d 1614 (Fed. Cir. 1999). The requirement for evidence of particularized motivation provides a safeguard against the "tempting but forbidden zone of hindsight." *Dembiczak* at p. 1616. Here, the asserted motivation (producing compounds with greater potency due to high specificity or binding) is so general that it could be asserted with respect to virtually any references in the biomedical field. The motivation identifies only a general desiderata without pointing in the direction of any specific modifications of the Choo *et al.* reference that are required to achieve the present claims. Further, the asserted motivation is not supported by an evidentiary source. The Examiner has not identified where the asserted motivation is found in the cited references or elsewhere. Absent the safeguards of either a specific motivation or an evidentiary source supporting the motivation, one cannot be assured that the combination of references was not the result of hindsight.

For these reasons, withdrawal of the rejection is respectfully requested.

7. Rejection under 35 USC 103

Claims 1-3, 6-7 and 9 stand rejected as obvious over Choo *et al.* (Current Opinion in Biotechnology) in view of Ogata and Hall for essentially the same reasons as the double patenting rejection.

Applicants traverse for the same reasons described above. In addition, the Choo *et al.* article (hereafter Choo *et al.* (2)) provides evidence teaching away from the presently claimed invention. The article indicates that simultaneously randomizing each of three zinc fingers in a three-finger zinc finger protein is "unlikely to be practical in the near future" due to the large number of permutations (p. 433, paragraph bridging cols. 1 and 2). Instead, the article proposes randomizing fingers individually and assembling zinc finger proteins from individually selected fingers (p. 433, second paragraph). The disclosure of randomizing zinc fingers individually and assembling selected zinc fingers in a modular fashion teaches away from simultaneously randomizing adjacent fingers, as required by the pending claims. For this reason, as well as the reasons given above, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 was amended as follows:

1. (Amended) A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to +9 with position +1 representing the first amino acid of a alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover [the overlap of a single pair of zinc fingers] at least one position selected from the group consisting of -1, 1, 2, 3, 5 and 6 and at least one position selected from the group consisting of -1, 1, 2 and 3 in first and second adjacent finger respectively.

Claim 7 was amended as follows:

7. (Amended) A library according to claim 1, wherein the randomization of amino acid residues is restricted such that the following amino acids [may] appear at the given positions:

Position	[Possible]Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D. A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E K, N, T

26. (New) The method of claim 1, wherein the randomization extends to at least positions 6 and 2 of the adjacent first and second zinc fingers respectively.

27. (New) A library according to claim 1 wherein at least positions -1, 1, 2, 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

28. (New) A library according to claim 1 wherein at least positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

ABSTRACT

The invention relates to a zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger which has been at least partially randomized, and to a set of zinc finger polypeptide libraries which encode overlapping zinc finger polypeptides, each polypeptide comprising more than one zinc finger which has been at least partially randomized, and which polypeptides may be assembled after selection to form a multifinger zinc finger polypeptide.

Claims

1. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover the overlap of a single pair of zinc fingers.

2. A library according to claim 1 wherein each polypeptide comprises between three and six zinc fingers.

3. A library according to claim 1 or claim 2, wherein one and a half zinc fingers are randomised in each polypeptide.

4. A set of zinc finger polypeptide libraries which encode overlapping zinc finger polypeptides, according to any one of claims 1 to 4, wherein the polypeptides may be assembled after selection to form a multifinger zinc finger polypeptide.

5. A set according to claim 4, comprising a pair of libraries encoding three-zinc finger polypeptides.

6. A library or set of libraries according to any preceding claim, wherein the randomised positions are selected from positions -1, 1, 2, 3, 5 and 6.

7. A library according to any preceding claim, wherein the randomisation of amino acid residues is restricted such that the following amino acids may appear at the given positions:

Position	Possible Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D, A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E, K, N, T